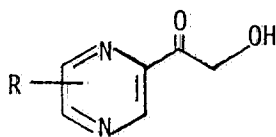


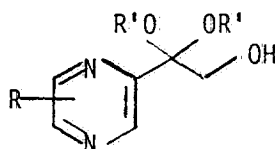
CHARGE NUMBER: 2520
PROJECT TITLE: Synthesis of Flavorants
PROJECT LEADER: William B. Edwards, III
PERIOD COVERED: February 1-28, 1983
DATE OF REPORT: March 7, 1983

I. Heteroaromatic Flavorants

A mixture of 2-oxo-2-(5- and 6-methylpyrazinyl)ethanol (I and II, 1:10 ratio) was synthesized in two steps from 2-acetyl-5- and 6-methylpyrazine via the dimethoxyketals (III and IV). Preliminary GC/MS analysis strongly indicated that I and II are pyrolysis products of 2,5- and 2,6-deoxyfructosazine, respectively.¹ Initial attempts to prepare I and II by hydrolysis of the diethoxyketals (V and VI) yielded only a trace amount of the desired products. Additionally, 2-acetyl-3-ethylpyrazine was hydroxylated to give the diethoxyketal (VII). Hydrolysis of VII to the corresponding hydroxyketone will be attempted. Compounds I through VII will be evaluated for their cigarette flavor properties. All had no appreciable odor at room temperature.²



I, R = 5-CH₃
II, R = 6-CH₃



III, R = 5-CH₃, R' = CH₃
IV, R = 6-CH₃, R' = CH₃
V, R = 5-CH₃, R' = C₂H₅
VI, R = 6-CH₃, R' = C₂H₅
VII, R = 3-C₂H₅, R' = C₂H₅

The following potential flavorants were placed in the CR file.³

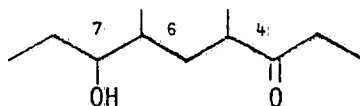
CR-2245 - 2-Acetoxy-6-methylpyrazine
CR-2278 - 2-Acetoxy-3-methylpyrazine
CR-2279 - Isoquinoline N-oxide

II. Entomological Research

Initial equilibration studies carried out on (+)-serricornin (VIII) showed no change in isomer ratio detectable by NMR analysis.⁴ This result strongly indicates that isolated VIII is fully equilibrated at the 4 carbon. While it has been

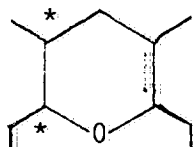
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reported by others that VIII is readily epimerized at the 4 position, this needs to be confirmed by us in order to complete the development of a stereocontrolled synthesis of VIII.²



VIII

A method for the large scale preparation of anhydroserricornin has been established. Compound IX can be synthesized in 77% yield by acid catalyzed dehydration of (+)-serricornin (VIII) in the appropriate solvent. These results far exceed existing literature methods which gave IX in about 25% yield. Compound IX is obtained as a mixture of two diastereomers in a 2:1 ratio. The chiral centers (*) of IX correspond to the 6 and 7 carbons of VIII. The isomer ratio at carbons 6 and 7 is reproducibly fixed in an earlier synthetic step and should not be altered by the subsequent chemistry. Consequently, our method should consistently yield IX with the same diastereomer ratio.²



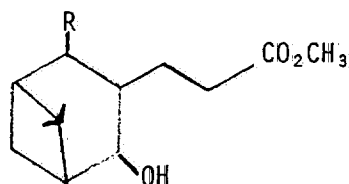
IX

The two step synthesis of 2,4-dimethyl-5-oxoheptylnitrile (X) developed last month was carried out on a 2.3 molar scale. Little variation in reaction yield was noted. Isomer equilibration/reduction of X gave 5-hydroxy-2,4-dimethylheptylnitrile (XI) with the same diastereomer ratio as previously obtained. Using liquid chromatography, XI was separated into two isomer fractions. Analysis of the fractions by nuclear magnetic resonance⁴ showed that one was a single diastereomer of XI while the other was a mixture of three isomers.²

III. Terpenoid Flavorants

Cembrenoid Flavorants: Reduction of methyl 3-[3-(6,6-dimethyl-2-oxobicyclo-[3.1.1]heptyl)]propionate (XII) and methyl 3-[3-(4,6,6-trimethyl-2-oxobicyclo-[3.1.1]heptyl)]propionate (XIII) gave the corresponding alcohols (XIV and XV). These alcohols will be evaluated for their cigarette flavor properties.³

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XIV, R = H

XV, R = CH₃

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